does not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 1-2, 4 and 7-16 will be pending.

Detailed Action

The Examiner stated that applicants' Amendment, filed 2/4/2002, Paper No.9, has been entered. The Examiner stated that claim 3 has been canceled; claims 1, 2 and 16 have been amended. The Examiner alleged that with regard to election of the subject to which the method will be administered, a transgenic non-human animal, was made **without** traverse in Paper No. 6. The Examiner stated that after further consideration, the requirement for an election of subject is withdrawn, as such, the Examiner will consider both a transgenic non-human animal and human subject with regard to the claimed invention. The Examiner stated that claims 1, 2 and 4-16 are under current examination. The Examiner stated that any rejection made of record in the prior Office action, mailed /20/01, Paper No. 7, and not made of record in the instant Office action, has been withdrawn in view of Applicants amendments to the claims.

Provisional Double Patenting under 35 U.S.C. §101:

The Examiner provisionally rejected claims 1-16 under 35 U.S.C. §101 as claiming the same invention as that of claims 1-16 of co-pending Application No. 09/992,955. The Examiner stated that this is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

In response, applicants request that the Examiner continue to hold this provisional rejection in abeyance until one of the two applications is allowed. Furthermore, applicants point out that subject to this application being otherwise allowable and copending application Serial No. 09/992,955 being allowed, applicants would consider filing a Terminal Disclaimer.

Rejection under 35 USC §112, first paragraph:

The Examiner maintained the prior rejection of claims 1, 2 and 4-16 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of decreasing cerebral vasoconstriction and ameliorating neurovascular stress in a transgenic mouse which overexpress mutant human amyloid beta precursor protein (APP), bearing the double mutation Lys670Asn and Met 671Leu, (TG APP sw +/- mice) by administration of a soluble receptor for advanced glycation endproduct (sRAGE), does not allegedly provide enablement for methods of decreasing cerebral vasoconstriction, ameliorating neurovascular stress or treatment of amyloid angiopathy in all transgenic non-human animal subjects or in a human subject by administration of any inhibitor of RAGE. The Examiner alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Examiner alleged that the claimed invention is directed to a method for decreasing cerebral vasoconstriction in a subject

suffering from chronic or acute cerebral amyloid angiopathy which comprises administering to the subject an inhibitor of receptor for advanced glycation endproduct (RAGE) to inhibit transcytosis of amyloid-â (Aâ) peptides across the blood-brain barrier in the subject (claim 1). The Examiner alleged that the claimed invention is further directed to a method for ameliorating neurovascular stress in a subject, comprising administering to the subject an inhibitor of RAGE to increase cerebral blood flow (claim 12). The Examiner alleged that the claimed invention is additionally directed to a method of treating amyloid angiopathy in a subject comprising administering to the subject an inhibitor of RAGE to increase cerebral blood flow (claim 16). The Examiner stated that in particular, the elected inhibitor RAGE is soluble RAGE (sRAGE).

The Examiner alleged that the specification teaches that administration of an inhibitor of RAGE can be used to treat subjects suffering from chronic or acute cerebral amyloid angiopathy, ameliorate neurovascular stress, or in the treatment of amyloid angiopathy (see p. 7, 1st paragraph, p.8 paragraphs 1 and 3). The Examiner alleged that the specification specifically teaches the blocking of RAGE in wild-type mice infused with synthetic amyloid-beta (Aâ) peptides by the use of an antibody against RAGE (á-RAGE), and soluble RAGE (sRAGE), which resulted in the suppression of binding and uptake of Aâ in relation to the vessel wall, and inhibited Aâ-induced cellular stress (see Example 1, and particularly p.34). The Examiner alleged that the specification teaches that Aâ transport to the brain was

significantly inhibited by á-RAGE and abolished by sRAGE and that several other molecular reagents were used to test effects on blood brain barrier (BBB) transport or the binding of Aâ (see p. 32). The Examiner alleged that the specification teaches that transgenic mice that overexpress mutant Aâ precursor protein (APP) (TG APP sw+/- mice) have a significant decrease in basal cerebral blood flow (CBF) values, and that infusion of á-RAGE increased the CBF in these mice. The Examiner alleged that the specification teaches that systemic administration of á-RAGE to these transgenic mice ameliorated cellular stress in the brain (see p.33, lines 11-29). The Examiner alleged that the specification further teaches that an acute model in mice that had Aâ-induced cellular stress and sustained reductions in CBF was blocked by circulating á-RAGE, and in TG APP sw+/-mice, CBF was blocked by circulating á-RAGE in a dose-dependent fashion (see Example 2).

The Examiner stated that although the specification does not explicitly teach the use of sRAGE administration to the TG APP sw+/-mice, Morser *et al.* (WO 97/39121, 23 October 1997) allegedly teach that both antibodies to RAGE and soluble sRAGE are capable of blocking or inhibiting the interaction between RAGE and its ligands (AGEs) in such diseases as diabetes and Alzheimer's disease (see p. 9, 2nd paragraph and Examples 2 and 4). The Examiner alleged that to this end, one would have a reasonable expectation of success in using sRAGE to increase CBF and ameliorate cellular stress in TG APP sw+/- mice. The Examiner stated that as such, the claimed invention is allegedly enabled for methods for decreasing cerebral

vasoconstriction and ameliorating neurovascular stress in a TG APP sw+/-mice by the administration of sRAGE as indicated above.

The Examiner alleged that applicants state that to expedite prosecution of the application, Applicants have amended claim 2 to recite, wherein the subject is a human subject (see p. 10, last paragraph of the Response). The Examiner alleged that Applicants further argue, as the subject is a human subject, this amendment obviated the Examiner's objection regarding the alleged limitations of transgenic technology (see p.11, last paragraph of the Response). The Examiner alleged that applicants elected a transgenic non-human animal as a species election **without** traverse in Paper No. 6. The Examiner stated that after further consideration, the Examiner withdraws this election requirement, and as such, the claimed invention is examined with regards to both a transgenic non-human animal and a human subject.

The Examiner stated that the prior rejection of claims 1 and 3-16 is maintained, because it is reiterated that the specification fails to teach methods of decreasing cerebral vasoconstriction and amelioration of neurovascular stress in any other transgenic non-human animal other than the exemplified TG APP sw+/- mice. The Examiner alleged that the specification fails to provide any relevant teachings or guidance with regard to the production of a transgenic non-human animal as claims, one of skill would not be able to rely on the state of the transgenic art for an attempt to produce all transgenic animals which over-express mutant human Aâ

precursor protein. The Examiner stated that the Examiner has provided the unpredictable state of the art for transgenics advanced on pages 5-8 of the prior Office action. The Examiner alleged that applicants have not provided evidence to overcome the unpredictabilities associated with the art of transgenics, and as such, it would have required undue experimentation for on skilled in the art to predict the results achieved in any host animal comprising and expressing a mutant human amyloid beta precursor protein transgene, the levels of the transgene product, the consequences of that product, and the resulting phenotype.

The Examiner stated that applicants traverse the Examiner's comments alleging a lack of guidance or teaching for the treatment of amyloid angiopathy in the present application (see p. 11, 2nd paragraph of the Response). The Examiner alleged that claim 16 has now been amended to recite a method for treating Alzheimer's disease. The Examiner alleged that applicants further contend that transgenic mouse models of AD-type pathology support the use of a RAGE inhibitor to decrease cerebral vasoconstriction and ameliorate neurovascular stress in such mice as a therapeutic model for treating AD in a human subject (see p. 12, paragraphs 2-3 of the Response).

The Examiner stated that applicants further submit various papers to support that transgenic mice with AD-type pathology may be useful in identifying method of treatment of AD in a human subject. The Examiner noted that these references, Exhibits B-F, (see pp.

12-16 of the Response) have allegedly not been included with Applicants' response, and as such have not been considered. The Examiner stated that furthermore, it is noted that applicants' Supplemental Information Disclosure Statement, filed 2/21/02, Paper #10, provide the art that was cited by the Examiner in the prior Office action.

The Examiner reiterated that the Examiner's comments are not directed to the fact that transgenic mice with AD-type pathology are not useful in the treatment of AD, rather, the Examiner's comments are directed to the claimed embodiment of claim 16 with regard to the decreasing cerebral vasoconstriction in a subject suffering from Alzheimer's disease. The Examiner alleged that the specification has only provided teachings to enable methods of decreasing cerebral vasoconstriction and amelioration of neurovascular stress in transgenic mice which overexpress mutant human amyloid beta precursor protein (APP), bearing the double mutation Lys670Asn and Met 671Leu, (TG APP sw+/-mice) by administration of a soluble receptor for advanced glycation endproduct (sRAGE).

The Examiner alleged that in view of the lack of guidance and direction in the specification for the use of sRAGE to decrease cerebral vasoconstriction or ameliorate neurovascular stress in any other species other than TG APP +/-mice, the unpredictable and undeveloped state of the art with respect to transgene behavior in transgenic animal subjects of all species, it would have required

undue experimentation for one skilled in the art to carry out the claimed methods, animals and use thereof.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that it would not have required undue experimentation to carry out the claimed invention. Applicants contend that the Examiner has failed to provide any evidence that would rebut the applicants reasonable correlation between the disclosed *in vivo* utility of the present claims and the *in vivo* animal model data recited in the specification.

Initially, applicants respectfully direct the Examiner to M.P.E.P. §2163(III)(A) which recites as follows:

> "A description is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption."

Applicants contend that the Examiner has failed to present any evidence rebutting the disclosure of the present invention. The disclosure recites that the treatment of cerebral vasoconstriction in the Hsaio mouse model of the present invention is "powerful in terms of its implications since the mice are considered a **model of Alzheimer's-type pathology**" [emphasis added]. See page 34, lines 8-10. In contrast, the Examiner fails to provide any evidence to rebut this fact and merely argues that "the specification has only provided teachings to enable methods of decreasing cerebral vasoconstriction and amelioration of neurovascular stress in transgenic mice which overexpress mutant human amyloid beta

precursor protein (APP)." See paper 11, page 8, paragraph 1.

In addition, applicants contend that the *in vivo* administration of sRAGE to Hsaio mice, a model of an Alzheimer's-type pathology, inhibited Aβ induced cerebral vasoconstriction, an Alzheimer's-type pathology in humans. The disclosure recites that "our current study demonstrates that RAGE mediates *in vivo* transcytosis of Aβ1-40 and Aβ-42 across the blood brain barrier (BBB) in mice. RAGE-dependent BBB transport of Aβ was coupled to its rapid neuronal uptake, induction of cellular stress and transient, but significant suppression of cerebral blood flow (CBF)." See page 31, lines 11-16 Further, the disclosure recites that the administration of either sRAGE or anti-RAGE IgG "inhibits Aβ-induced cell stress in the vasculature and in neurons, consequent to systemic infusion of Aβ" See page 34, lines 9-14.

Therefore, applicants contend that based upon the applicants use of an art accepted murine model of an AD-type pathology in a human, the relevant evidence as a whole demonstrates a reasonable correlation between the disclosed *in vivo* utility of the present claims and the *in vivo* animal model data recited in the specification. Accordingly, it would not have required undue experimentation to carry out the claimed invention. Applicants contend that these comments obviate the Examiner's above rejection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $460.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

10/24/02
John P. White Date
Reg. No. 28,678

John P. White
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Exhibit A:

--1. (2x amended) A method for decreasing cerebral vasoconstricition in a subject suffering from an Alzheimer's disease-type pathology, which comprises administering to the subject an inhibitor of receptor for advanced glycation endproduct (RAGE) in an effective amount to inhibit transcytosis of amyloid-β peptides across the blood-brain barrier in the subject, thereby decreasing cerebral vasoconstriction in the subject.--